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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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Cardiovascular System. The cardiovascular effects of muscarinic receptor antagonists are of limited clinical application. Generally, these agents are used in coronary care units for short-term interventions. Atropine is a specific antidote for the cardiovascular collapse that may result from the injudicious administration of a choline ester or an inhibitor of cholinesterase. It also is used to antagonize reflex vagal cardiac slowing.

Atropine may be of value in the initial treatment of patients with acute myocardial infarction in whom excessive vagal tone causes sinus or nodal bradycardia. Sinus bradycardia is the most common arrhythmia seen during acute myocardial infarction, especially of the inferior or posterior wall. Some experimental and clinical evidence suggests that bradycardia may be beneficial in limiting the size of the infarction and protecting the ischemic myocardium against ventricular arrhythmias and fibrillation (De Ferrari *et al.*, 1994). On the other hand, severe bradycardia may lead to hypotension, and patients with very high vagal tone may develop AV block. Atropine may prevent further clinical deterioration in such cases by restoring heart rate to a level sufficient to maintain adequate hemodynamic status and to eliminate AV nodal block. Dosing must be done judiciously; doses that are too low can cause a paradoxical bradycardia (*see* above), while excessive doses will cause tachycardia that may extend the infarct by increasing the demand for oxygen.

Atropine occasionally is useful in reducing the severe bradycardia and syncope associated with a hyperactive carotid sinus reflex. It has little effect on most ventricular rhythms. In some patients atropine may eliminate premature ventricular contractions associated with a very slow atrial rate. It may also reduce the degree of AV block when increased vagal tone is a major factor in the conduction defect, such as the second-degree AV block that can be produced by digitalis. Atropine also is used diagnostically to evaluate autonomic control of SA and AV nodal function.

Central Nervous System. For many years the belladonna alkaloids and subsequently the tertiary-amine synthetic substitutes were the only agents helpful in the treatment of parkinsonism. Levodopa or levodopa along with carbidopa now is the treatment of choice, but alternative or concurrent therapy with muscarinic receptor antagonists may be required in some patients (*see* Chapter 22). Centrally acting agents such as benztropine have been shown to be efficacious in preventing dystonias or parkinsonian symptoms in patients treated with antipsychotic drugs (Arana *et al.*, 1988; *see* also Chapter 18). Instilling a low dose of the muscarinic antagonist tropicamide in the eyes of patients with a probable diagnosis of Alzheimer's disease has been reported to demonstrate a marked hypersensitivity in pupil dilation (Scinto *et al.*, 1994). This unexplained but potentially noninvasive screen for the disease may provide clues concerning changes in receptor sensitivity associated with the condition.

The belladonna alkaloids were among the first drugs to be used in the prevention of motion sickness. Scopolamine is the most effective prophylactic agent for short (4- to 6-hour) exposures to severe motion, and probably for exposures of up to several days. All agents used to combat motion sickness should be given prophylactically; they are much less effective after severe nausea or vomiting has developed. A preparation for the transdermal administration of scopolamine (TRANSDERM SCOP) has been shown to be highly effective for the prevention of motion sickness. The drug is incorporated into a multilayered adhesive unit that is applied to the postauricular mastoid region. Absorption of the drug is especially efficient in this area. For optimal effects, the application should be made at least 4 hours before the antiemetic effect is required. The duration of action of the preparation is about 72 hours, during which time approximately 0.5 mg of scopolamine is delivered. Dry mouth is common, drowsiness is not infrequent, and blurred vision occurs in some individuals. Rare but severe psychotic episodes have also been reported (Wilkinson, 1987; Ziskind, 1988).

The use of scopolamine to produce tranquilization and amnesia in a variety of circumstances, including labor, is declining. Given alone in the presence of pain or severe anxiety, scopolamine may induce outbursts of uncontrolled behavior.

Uses in Anesthesia. The belladonna alkaloids commonly were used to inhibit excessive salivation and secretions of the respiratory tract induced by administration of general anesthetic agents; their concomitant bronchodilator action also was of value. The increasing use of relatively nonirritating anesthetics has virtually eliminated this use of muscarinic receptor antagonists. Scopolamine may contribute to tranquilization and amnesia. Atropine commonly is given to prevent vagal reflexes induced by surgical manipulation of visceral organs. Atropine also is used with neostigmine to counteract its parasympathomimetic effects when the latter agent is used to reverse muscle relaxation after surgery (*see* Chapter 9). Serious cardiac arrhythmias have occasionally occurred, perhaps because of the initial bradycardia produced by atropine combined with the cholinomimetic effects of neostigmine.

Genitourinary Tract. Atropine often has been given with an opioid in the treatment of renal colic in the hope that it will relax the ureteral smooth muscle; however, as in biliary colic, it probably does not make a major contribution to the relief of pain. The belladonna alkaloids and several synthetic substitutes can lower intravesicular pressure, increase capacity, and reduce the frequency of urinary bladder contractions by antagonizing the parasympathetic control of this organ. The block is less complete than in many other organs, but it has been taken as a basis for the use of such agents in enuresis in children, particularly when a progressive increase in bladder capacity is the objective; to reduce urinary frequency in spastic paraplegia; and to increase the capacity of the bladder in conditions in which irritation has led to hypertonicity (Wein, 1991). However, it has not been established that muscarinic receptor antagonists make a major contribution to the treatment of any of these conditions. Oxybutynin appears to be effective in the treatment of a range of unstable bladder conditions (Kirkali and Whitaker, 1987) but has relatively less anticholinergic and greater antispasmodic activity than atropine.

Anticholinesterase and Mushroom Poisoning. The use of atropine in large doses for the treatment of poisoning by anticholinesterase organophosphorus insecticides is discussed in Chapter 8. Atropine also may be used to antagonize the parasympathomimetic effects of neostigmine or other anticholinesterase agents administered in the treatment of myasthenia gravis. It does not interfere with the salutary effects at the skeletal neuromuscular junction, and it is particularly useful early in therapy, before tolerance to muscarinic side effects has developed.

As discussed earlier, atropine is only useful as an antidote for the symptoms of mushroom poisoning due to the cholinomimetic alkaloid muscarine, found in certain mushroom species.

PROSPECTUS

The availability of cDNAs encoding five distinct muscarinic receptor subtypes has facilitated the development

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Piperidines (Prototype: Terfenadine). H_1 antagonists of this class include terfenadine, astemizole, and loratadine. These agents are highly selective for H_1 receptors and are devoid of significant anticholinergic actions. These agents also penetrate poorly into the CNS. Taken together, these properties appear to account for the low incidence of side effects of piperidine agents.

Therapeutic Uses

H_1 antagonists have an established and valued place in the symptomatic treatment of various immediate hypersensitivity reactions. In addition, the central properties of some of the series are of therapeutic value for suppressing motion sickness or for sedation.

Diseases of Allergy. H_1 antagonists are most useful in acute types of allergy that present with symptoms of rhinitis, urticaria, and conjunctivitis. Their effect, however, is confined to the suppression of symptoms attributable to the histamine released by the antigen–antibody reaction. In bronchial asthma, histamine antagonists have limited beneficial effects and are not useful as sole therapy (*see* Chapter 28). In the treatment of systemic anaphylaxis, in which autacoids other than histamine play major roles, the mainstay of therapy is epinephrine, with histamine antagonists having only a subordinate and adjuvant role. The same is true for severe angioedema, in which laryngeal swelling constitutes a threat to life.

Other allergies of the respiratory tract are more amenable to therapy with H_1 antagonists. The best results are obtained in seasonal rhinitis and conjunctivitis (hay fever, pollinosis), in which these drugs relieve the sneezing, rhinorrhea, and itching of eyes, nose, and throat. A gratifying response is obtained in most patients, especially at the beginning of the season when pollen counts are low; however, the drugs are less effective when the allergens are in abundance, when exposure to them is prolonged, and when nasal congestion has become prominent. Topical preparations of antihistamines such as levocabastine have been shown to be effective in allergic conjunctivitis and rhinitis (Janssens and Bussche, 1991). At present, a topical ophthalmic preparation of this agent is available in the United States (*see* Chapter 65) and nasal sprays are being tested.

Certain of the allergic dermatoses respond favorably to H_1 antagonists. Benefit is most striking in acute urticaria, although the itching in this condition is perhaps better controlled than are the edema and the erythema. Chronic urticaria is less responsive, but some benefit may occur in a fair proportion of patients. Furthermore, the combined use of H_1 and H_2 antagonists is effective for some individuals if therapy with an H_1 antagonist has failed. Angioedema also is responsive to treatment with H_1 antagonists, but the paramount importance of epinephrine in the severe attack must be reemphasized, especially in the life-threatening involvement of the larynx (*see* Chapter 10). Here, however, it may be appropriate to administer additionally an H_1 antagonist by the intravenous route. H_1 antagonists also have a place in the treatment of pruritus. Some relief may be obtained in many patients suffering atopic dermatitis and contact dermatitis (although topical corticosteroids are more valuable) and in such diverse conditions as insect bites and ivy poisoning. Various other pruritides without an allergic basis sometimes respond to antihistamine therapy, usually when the drugs are applied topically but sometimes when they are given orally. However, the possibility of producing allergic dermatitis with local application of H_1 antagonists must be recognized. Since these drugs inhibit allergic dermatitis, they should be withdrawn well before skin testing for allergies.

The urticarial and edematous lesions of serum sickness respond to H_1 antagonists, but fever and arthralgia often do not.

Many drug reactions attributable to allergic phenomena respond to therapy with H_1 antagonists, particularly those characterized by itch, urticaria, and angioedema; reactions of the serum-sickness type also respond to intensive treatment. However, explosive release of histamine generally calls for treatment with epinephrine, with H_1 antagonists being accorded a subsidiary role. Nevertheless, prophylactic treatment with an H_1 antagonist may suffice to reduce symptoms to a tolerable level when a drug known to be a histamine liberator is to be given.

Common Cold. Despite persistent popular belief, H_1 antagonists are without value in combating the common cold. The weak anticholinergic effects of the older agents may tend to lessen rhinorrhea, but this drying effect may do more harm than good, as may also the tendency to induce somnolence (*see* West *et al.*, 1975).

Motion Sickness, Vertigo, and Sedation. Although scopolamine, given orally, parenterally, or transdermally, is the most effective of all drugs for the prophylaxis and treatment of motion sickness, some H_1 antagonists are useful in a broad range of milder conditions and offer the advantage of fewer adverse effects. These drugs include dimenhydrinate and the piperazines (*e.g.*, cyclizine, meclizine). Promethazine, a phenothiazine, is more potent and more effective and its additional antiemetic properties may be of value in reducing vomiting, but its pronounced sedative action usually is disadvantageous. Whenever possible, the various drugs should be administered an hour or so before the anticipated motion. Dosing after the onset of nausea and vomiting rarely is benficial.

Some H_1 antagonists, notably dimenhydrinate and meclizine, are often of benefit in vestibular disturbances, such as Ménière's disease, and in other types of true vertigo (*see* Cohen and DeJong, 1972). Only promethazine has usefulness in treating the nausea and vomiting subsequent to chemotherapy or radiation therapy for malignancies; however, other effective antiemetic drugs are available (see Chapter 38).

Diphenhydramine can be used to reverse the extrapyramidal side effects caused by phenothiazines. The anticholinergic actions of this agent also can be utilized in the early stages of treatment of patients with Parkinson's disease (*see* Chapter 22), but it is less effective than other agents such as trihexyphenidyl (ARTANE).

The tendency of certain of the H_1-receptor antagonists to produce somnolence has led to their use as hypnotics. H_1 antagonists, principally diphenhydramine, often are present in various proprietary remedies for insomnia that are sold over the counter. While these remedies generally are ineffective in the recommended doses, some sensitive individuals may derive benefit (*see* Faingold, 1978). The sedative and mild antianxiety activities of hydroxyzine and diphenhydramine have contributed to their use as weak anxiolytics.

H_3-RECEPTOR AGONISTS AND ANTAGONISTS

Originally the H_3 receptor was described as a presynaptic receptor present on histaminergic nerve terminals in the CNS that exerted feedback regulation of histamine synthesis and release (Arrang *et al.*, 1983). Since then, H_3 receptors have been found to function in a wide variety of tissues. Like H_1 and H_2 receptors, H_3 receptors are G protein–coupled receptors; their occupation results in a decrease of Ca^{2+}